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St. John's Wort---An herbal myth or a botanical Miracle

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Abstract

Herbal products such as St. John's Wort are a multi-billion dollar industry word-wide. St. John's Wort has been widely used for treatment of several biological ailments, including depression. This paper focuses solely on the relationship between medicinal properties of St. John's Wort and its effectiveness as a treatment for depression. There have been many studies in US and Europe aimed at establishing the effectiveness of St. John's Wort as a natural remedy for depression. The results of these studies are mixed. While some individuals may experience relief from depression by taking St. John' Wort many do not.

Keywords

Psychotropic Drugs, Herbal Medicine, Medicinal Chemistry

1. Introduction

Major depressive disorder is a common ailment affecting millions of Americans. Major depression has a known lifetime prevalence of 15% in the United States. Depression is the main cause of suicide in the US--- about 70% of all suicides in the U.S. are traced directly to untreated cases of depression. It is now estimated that by the year 2020, suicide will be the tenth cause of death in the U.S. Epidemiologists suggest that at any given time, approximately 2 to 3 percent of the US population is hospitalized or is seriously impaired by a mood disorder, including depression. It is also estimated that approximately three times as many women as men are treated for or are candidates for developing depression. The cost of major depressive disorder to the US economy has been estimated to surpass 50 billion dollars per year. Even in the presence of an aggressive research agenda by a large number of researchers worldwide employing all the advances of modern medicine, depression remains a severely common and formidable human ailment with high mortality and morbidity of unknown etiology.

The main organic presentation of major depression consist of changes in the hypothalamic functions that have an influence on appetite for food, libido, circadian rhythms, and finally the synthesis and release of hypothalamic neurohormones. Those individuals suffering from major depression exhibit melancholic tendencies with decreased appetite, decreased sexual drive, sleep disturbances, mood swings, and endocrine abnormalities.

The treatment of depression with currently available pharmacological agents is only successfully achieved in about 65-70% of cases. Although many of the newly developed second-generation antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) have reduced the risks of unwanted side effects, in comparison to the older generation tricyclic (TCAs) antidepressants, the new generations of antidepressants have had little effect in terms of improving the effectiveness of the treatment.

Hundreds of studies are conducted each year in order to shed light on the function of various neurotransmitter systems that may be at the heart of the biological basis for major depression. Nonetheless, the proposed existing models, including that of monoamine hypothesis, do not explain fully the biology of depression. The search for new molecules of significance and new biological targets for

antidepressant drug discovery remain a formidable challenge for modern pharmacological research. However, such efforts are needed and must be pursued in order to understand the fundamental molecular mechanisms responsible for depression. These studies will be instrumental as a road map to point out new directions for treatment of depression.

There are investigations currently underway in order to understand the mechanisms of action for the observed therapeutic effects of herbal products such as St. John's Wort. These studies may uncover new mechanisms of action and new novel treatments for depression or other CNS disorders. Needless to say, central to these investigative efforts would be a better understanding of the St. John's Wort plant and its mood altering properties.

St. John's Wort is a natural herb used for alleviating the symptoms of depression. Its name comes from the fact that the plant flowers during the summer season on or around the St. John's day. This is on the 24th of June. Several preparations containing St. John's Wort are sold commercially in Europe. This herb is known by a few other names like St. John's Wort, hypericum, Klamath weed, and goatweed. The Latin name for this substance is *Hypericum perforatum*.

Hypericum extracts are among the most widely used antidepressants in Germany. In Germany, St, John's Wort accounted for a market share of more than 25% of all antidepressant prescriptions sold in 1997. Most of the research on Hypericum perforatum has been done in Germany and are published in European journals. Several randomized clinical studies have shown that Hypericum perforatum extracts were significantly superior to placebo and similarly effective as standard antidepressants in the treatment of mild to moderately severe depression. The major chemical components found in St. John's Wort consist of the following: Hypericin has a molecular Formula: C30H16O8, and Hyperforin has a molecular Formula C35H52O4. Hyperforin is one of the chemicals postulated to be responsible for some of the mood altering effects of St. John's Wort. It is found on the top part of the flower and is used for medicinal preparation. However, overall, there have been several chemical constituents that have been elucidated from the chemical analysis of St. Johns' Wort. These are: Ad-hyperforin, Dianthrone, Xanthones, and Flavonoids.

2. A Proposed Mechanism of Action fortheEffectiveness of St. John's Wort

Hyperforin is the substance that appears to show an effect on the Serotonergic, Dopaminergic, Noradrenic, and GABAergic systems. But Hyperforin's action on the brain's 5-HIAA and 5-HT levels appears not to be the same as the action of traditional 5-HT re-uptake blockers. The earlier studies claimed hypericin is the active constituent and demonstrated that hypericin inhibits monoamine oxidases (MAO A and MAO B). These are the enzymes responsible for the breakdown of noradrenaline and serotonin. The later studies have challenged the assertion that hypericin is in fact the active constituent responsible for Hypericum's actions. The more recent studies have claimed that hyperforin is the main antidepressant component of St. John's Wort. The antidepressant property of hyperforin has been attributed to its ability to increase the extracellular synaptic cleft levels of the monoamines, such as dopamine, noradrenaline, serotonin, and glutamate. This is most probably a consequence of reuptake inhibition. One may argue that it is possible that both hypericin and hyperforin have antidepressant properties; however, it is still unclear whether those are the only compounds that contribute to the antidepressant effects of Hypericum. Little is known about the effects of long-term administration of Hypericum, and about the effects of Hypericum perforatum at the molecular level (i.e. altering gene expression).

Some investigators now argue that all chemical components of St. John's Wort are required in order to maximize its medicinal effects on the Central Nervous System. The mechanism of action postulated for St. John's Wort appear to center on the inhibition of the synaptic re-uptake systems for serotonin, noradrenaline, and dopamine; Hypericum perforatum is also believed to produce monoamine re-inhibition and long-term changes in the central nervous system receptors.

Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter found in the central nervous system and the gastrointestinal tract, which is believed to play an important role in the modulation of anger, aggression, body temperature, mood, sleep, sexuality, and appetite. Dopamine is classified as a catecholamine. This is a class of molecules that serve as neurotransmitters and hormones. Dopamine is a precursor of adrenaline and a closely related molecule, noradrenaline. Dopamine is formed by the decarboxylation (removal of a carboxyl group) from dopa aminobutyric acid (GABA) is an amino acid neurotransmitter synthesized by decarboxylation of glutamate by the enzyme glutamic acid decarboxylase. It plays a role in regulating neuronal excitability throughout the nervous system. GABA is the main inhibitory neurotransmitter in the humans and a potent mediator of depression symptoms. There is evidence that the effects of Hypericum perforatum in the brain are consistent with effects reported for known prescription antidepressants.

The classical symptoms of depression are associated with feelings of melancholy, disinterest in the activities of daily living, boredom or lack of enjoyment in life, and feelings of self-doubt. Those who battle with these experiences often eat less than normal and report disturbances in their sleep pattern. Serotonin levels in the brain are often associated with the more classical symptoms of depression, and noradrenaline is often associated with the symptoms of fatigue commonly observed in depressed populations. It is these classical

symptoms of depression that many investigators believe will respond best to a regiment of St. John's Wort supplements.

However, it has been difficult to validate the postulated model underlying the mechanism of action some researchers have attributed to Hypericum perforatum. There is visible disagreement among researchers as to the exact mechanism of action for the antidepressant effects observed in some patients who reported improvement in their symptoms of depression after using St. John's Wort.

3. St. Johan's Wort Formularies

There are more than 370 species of the genus Hypericum known commercially as St. John's Wort. Several of the Hypericum species are not pharmacologically active and have no reported medicinal properties. There is debate as to the exact nature of the substances that are included in the commercially available St. John's Wort. This debate as resulted in the notion that not all St. John's Wort commercial formulation tables are equal. The vast majority of St. John's wort formulations sold in the health food stores are made with aerial parts, which are also known in the industry as "Grind". Grind is a whole ground up plant, not the small red and white dots in flowers that contain the important mood elevating chemicals. Grind does not contain hyperforin. Of even greater concern for the consumers, grind is believed to contain zanthrones found in the stems, which some have attributed to be the source of the MAO inhibitors. MAO inhibitors were believed to be the major cause of drug overdoses in the early forms of prescription antidepressants.

Based on the available evidence, St. John's Wort must contain both hypericin and hyperforin if is to be effective as a mood modulating agent. Hyperforin is only found in the red and white dots in the flowers.

Harvesting high hyperforin content is critical. At the time of harvest, the higher the hypericin content, the lower is the hyperforin level and vice a versa. Extracting high quality hyperforin is difficult and costly for the herbal supplement industry. First the plant must be of superior quality. The crop should preferably be grown using non-phosphate fertilizers. Upon harvest the flowers must be carefully dried so the hyperforin can be extracted using methanol extraction process. Hyperforin is a very delicate substance and can be easily destroyed by exposure to oxygen, heat, or moisture.

The strength and quality of herbal products are often unpredictable. Products can differ in contents not only from brand -to- brand, but also from batch- to -batch. Information on labels may be misleading or inaccurate to be of any use to consumers. The U.S. Food and Drug Administration (FDA) classifies herbal products such as St. John's Wort as dietary supplements. FDA is a regulatory agency of the Federal Government. The FDA's requirements for testing and obtaining approval to sell dietary supplements are far less strict and its industry oversight far less stringent than its requirements for commercially sold prescription drugs.

With the increased awareness of harmful effects and health hazards posed by some natural product supplements, there is a renewed call for a greater government oversight of the health food industry. However, these calls have not yet materialized into substantive government regulation of the multi-billion dollar herbal supplement industry.

4. Recommended Dosage

Modern extracts of St. John's Wort are typically sold and standardized to 0.3% Hypericins. The reason has to do with the fact that this compound is believed to be more stable than its counterpart, Hyperforin. However, it now appears that Hyperforin extract, regardless of its standardization to 3.0%, 5.0% or 10.0%, is highly unstable. Based upon further chemical analysis of St. John's Wort extracts containing Hyperforin derivatives, there is clear evidence of rapid breakdown of Hyperforin. Further studies of St. John's Wort extracts containing Hyperforin derivatives concluded that regardless of the particular standardization level, Hyperforin extracts decreased to their naturally occurring level of 3.0%~4.0% concentration in all cases.

For St. John's Wort, the recommended dose varies from product- to- product. Each manufacture appears to have its own unique recommended dose. The standard dosage of St. John's Wort is 300 mg 3 times a day of an extract standardized to contain 0.3% hypericin. However, a few new products on the market are standardized to Hyperforin content. These newer products are standardized to usually 2 to 3% Hyperforin instead of Hypericin. These are taken at the same dosage as those preparations standardized to Hypericin. Some users take 500 mg twice a day, or 600 mg in the morning and 300 mg in the evening. Some people have reported experiencing GI irritations if St. John's Wort is taken on an empty stomach. Manufactures state that the herb may be taken with food or on an empty stomach. The full effect of St. John's Wort would not be realized until after at least four weeks of intake.

5. Adverse Drug Interaction with Concomitant Administration of St. John's Wort

It is recommended that St. John's Wort be taken under supervision of a physician because adverse drug-drug interactions have been reported. St. John's Wort appears to decrease the blood levels of some concomitantly administered drugs. This effect may be due to the induction of enzymes in the cytochrome P450 biotransformation pathway and/or the P-glycoprotein transporter. Substances that induce drug metabolism decrease the plasma concentration of co-administered drugs that are substrates for those same biotransformation enzymes. Induction can be expected to reduce the

therapeutic effects of medicines that are deactivated by biotransformation enzymes and to increase the pharmacodynamic effects of prodrug that are activated as a result of metabolism.

In a study preformed by the National Institutes of Health (NIH), the concomitant administration of St. John's Wort with indinavir (Crixivan), an HIV-1 protease inhibitor for the treatment of HIV infection, caused a substantial decrease of indinavir plasma concentrations. The results of this study were published in the February 12, 2000, issue of Lancet.

Although adverse drug interaction studies for St. John's Wort are not yet available for antiretroviral agents other than indinavir, the possibility of significant reduction in the blood concentrations of all of currently available HIV-1 protease inhibitors (PIs) must be considered if taken in combination with St. John's Wort. Moreover, the possibility of adverse reactions with other drugs that are similarly metabolized, including the non-nucleoside reverse transcriptase inhibitors (NNRTIs) cannot be ignored. The concomitant use of St. John's Wort with PIs or NNRTIs is, therefore, not recommended because of the risk of reduced antiretroviral drug concentrations that could lead to therapeutic failure and result in the development of viral strains resistant to the administered drug as well as other members of its therapeutic class.

Another study has demonstrated decreased levels of the cardiac glycoside, digoxin, if taken at the same time as St. John's Wort. Other adverse drug interactions with St. John's Wort have been demonstrated in different published reports. For those patients with organ transplants who take the immunosuppressant, cyclosporine, together with St. John's Wort, there is reported danger that patients may experience acute graft rejection due to the decreased blood levels of cyclosporine. The use of St. John's Wort with the anticoagulant drug, Warfarin, has been reported to reduce the drug's anticoagulant effect. In these patients, the Warfarin dosage level must be adjusted upward in order to counteract the adverse effects of St. John's Wort.

A different study raises concerns about adverse interactions between St. John's Wort and the asthma medication, theophylline. The incidents of breakthrough bleeding in some patients receiving St. John's Wort together with oral contraceptives may increase the risk of unwanted pregnancies in patients taking oral contraceptive agents together with St. John's Wort.

St. John's Wort has also been shown to inhibit the neuronal reuptake of serotonin and certain other neurotransmitters in the brain. When St. John's Wort is administered together with prescription antidepressant drugs that also increase the availability of serotonin in the brain, individuals taking this combination may experience a pattern of symptoms known as serotonin syndrome. Serotonin syndrome presents with nausea, vomiting, restlessness, dizziness, tremor and headache. There are published reports that have described the occurrence of serotonin syndrome when St. John's Wort was used at the same time as certain prescription antidepressant drugs such as selective serotonin reuptake inhibitors and nefazodone.

There are many more drugs that may be candidates for adverse drug interactions with St. John's Wort and those candidates are not limited to the medications mentioned in this paper. As research into adverse drug interaction with St. John's Wort continues, it is likely that the list of known and suspected adverse interactions will continue to grow and may include an array of other drugs that are metabolized by the same hepatic enzymes.

6. Consumer Appeal

St. John's Wort is commonly used in Europe as the herbal remedy choice for depression. In the United States, St. John's Wort is not a prescription medication. It is considered an herbal remedy with considerable public interest in it. St. John's. Today, St. John's wort remains among the top-selling herbal products in the United States.

For some patients who take antidepressant drugs,those drugs are not effective and patients do not experience relief from their prescription medication. They report adverse side effects such as a dry mouth, nausea, headache, or increased effects of depression. Other patients report unpleasant and unwanted side effects they attribute to their medication. These unwanted side effects include symptoms associated with sleep and sexual dysfunction.

Sometimes people simply turn to herbal products like St. John's wort because they believe "natural" products are better for them than prescription medications. Some mistakenly believe natural products are always safer than prescription medications. However, this belief is not completely true. Finally, for many cost of herbal remedies can be the chief reason for their utilization because St. John's wort costs less than many antidepressant medications and it is obtained without a prescription.

7. Environmental Factors Affecting the Cultivation of St. John's Wort

Hypericum perforatum L. (St. John's Wort), a traditional herb with antidepressive and wound healing properties is being examined in light of environmental factors that affect secondary metabolite production. The secondary metabolite of St. John's Wort is influenced by temperature, light, and light intensity. The most optimal temperatures for hyperforin content per plant appear to be in the range of 25-30C. Relatively high (35 degrees C) or low (15 degrees C) temperatures reduces the photosynthetic efficiency of the leaves in St. John's Wort plants and resulted in low CO2 assimilation. The soil mineral nutrients play a part in secondary metabolite production in St. John's Wort. Great variability is observed in the secondary metabolites obtained from naturally growing plants, which is due to environmental variability, and biotic and abiotic contamination during cropping. There is also a seasonal variation during which peak secondary metabolites levels

may be observed. The wild type plants and their bioactive secondary metabolites even show great regional variability, a characteristic that may be easily studied by identifying the specific locations where these plants normally grow. It should be mentioned, however, that extreme variability in observed secondary metabolites is generally applicable to all naturally growing plants with medicinal properties. In that sense, St, John's Wort plant is not unique.

The environmental concentration of CO_2 is a major contributing factor in the ultimate yield observed in the biosynthesis of secondary metabolites in St, John's Wort plants. In a high-CO_2 enriched environment, the plant 's concentrations of hypericin and pseudohypericin (two of the major health-promoting substances in the plants) increases by more than 100%.

Depending on environmental and climatic conditions, St John's Wort plants show environmental adaptability in order to promote their survival. The plant exhibits an ability to dominate its ecosystem, which further aids in its survival. Like any other plant species, ST. John's Wort is susceptible to herbicides damage, resulting in diminished biosynthesis of secondary metabolites. The plant's seed is able to stay in the soil for long periods and germinate anew following an environmental disturbance. This adds to the plants' resiliency following a natural or a man-made disaster.

Bioactive metabolites in St. John's Wort are vulnerable to contamination by inorganic chemicals such as nickel. Controlled studies have shown that when this plant is contaminated with nickel, it completely looses its ability to form active secondary metabolites.

Pathogenic infections are seen in plants and are the results of bacterial or viral infestations. When this occurs in St. John's Wort plants, the biosynthesis of the biochemically active secondary metabolites are significantly affected. In general, the yield obtained per plant is significantly reduced in infested plants when compared to their healthy counterparts.

The general effects of climate change appear to be impacting plants in all regions of the world. For example, evidence indicates that climate change has been affecting vegetation patterns such as phenology and distribution. The timing of a plant's life cycle can affect whether it reaches optimal seed set before the end of the growing season. The general effects of climate change worldwide should be viewed as additional factors that could affect the St. John's Wort plants and their ability to produce secondary metabolites of medicinal interest. It will be difficult for any plant to escape some of the inevitable adverse consequences associated with climate change. And St. Johns Wort plant is not an exception.

8. Conclusion

Although clinical trials on the effects of St. John's Wort have shown some promise, the usefulness of these studies are somewhat hampered by the fact that an exact mechanism of action for St. John's Wort is yet to be elucidated. Until scientific evidence emerges that elucidates the exact mechanism of action for this Botanical substance, further mood enhancing research will be severely limited as will any effort to standardize St. John's Wort dietary supplements. Hence, we still have a long way ahead before we can declare victory for St. John's Wort as being equivalent to prescription mood enhancers.

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